Common Drug Review
Pharmacoeconomic Review Report

December 2014

Drug	Standardized Allergenic Extract, Timothy grass (*Phleum pratense*) (Grastek) (sublingual tablet 2,800 BAU)
Indication	Reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific immunoglobulin E, and who have responded inadequately or are intolerant to conventional pharmacotherapy.
Listing Request	Treatment of patients with Timothy and related grass pollen-induced allergic rhinitis with or without conjunctivitis, in adults and children five years of age and older.
Manufacturer	Merck Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

ABBREVIATIONS

5GPAE	five-grass pollen allergen extract
AA	allergic asthma
AR	allergic rhinitis
BAU	bioequivalent allergy unit
CI	confidence interval
DB	double-blind
IR	index of reactivity
NMA	network meta-analysis
PPAE	*Phleum pratense* allergen extract
QoL	quality of life
SCIT	subcutaneous immunotherapy

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Standardized Allergenic Extract, Timothy grass (*Phleum pratense*) (Grastek) (sublingual tablet 2,800 BAU)**
Study Question	Assess the cost-effectiveness of Grastek compared with symptomatic treatment and 5GPAE for the treatment of grass pollen-induced AR
Type of Economic Evaluation	• CUA • CMA
Target Population	Patients who suffer from moderate or severe seasonal AR to grass pollen
Treatment	• CUA: Grastek used daily continuously for three years • CMA: Grastek used for at least eight weeks pre-season and dosing maintained throughout the allergy season
Outcome(s)	• CUA: QALYs, costs • CMA: costs
Comparators	• CUA: Symptomatic treatment and 5GPAE • CMA: SCIT (perennial and seasonal) and 5GPAE
Perspective	Public payer
Time Horizon	• CUA: five years • CMA: three years

Manufacturer's Results (Base Case)	• CUA:
	  ○ Grastek has an ICUR of $36,035 per QALY vs. symptomatic treatment
	  ○ Grastek has an ICUR of $33,098 per QALY vs. 5GPAE
	• CMA: Grastek is cost saving vs. perennial SCIT, seasonal SCIT, and 5GPAE

Key Limitations and CDR Estimate(s)	• Outdated drug prices for Grastek and 5GPAE were used in the economic analyses. • In the CUA, issues were identified with the model structure and unsupported assumptions were included (e.g., 5GPAE would not sustain its efficacy beyond the treatment period). CDR reanalysis, with equal post-treatment efficacy for both 5GPAE and Grastek based on the results of the manufacturer's network meta-analysis, showed that only cost differences exist between treatments. • Based on a pollen season that could range from two to six months with 8 to 16 weeks of pre-season treatment with PPAE, the three-year incremental cost of PPAE (per patient) ranged from a cost saving of $1,717 to a cost impact of $245 compared with perennial SCIT, and a cost saving of $97 to a cost impact of $1,864 compared with seasonal SCIT. PPAE was associated with cost savings ranging from $400 to $837 compared with 5GPAE.

5GPAE = 5-grass pollen allergen extract (Oralair); AR = allergic rhinitis; BAU = bioequivalent allergy unit; CDR = Common Drug Review; CMA = cost-minimization analysis; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; PPAE = *Phleum pratense* allergen extract; QALY = quality-adjusted life-year; SCIT = subcutaneous immunotherapy.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Grastek (Standardized Allergenic Extract, Timothy grass; *Phleum pratense* allergen extract [PPAE]) is an immunotherapy indicated for reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis in adults and children five years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* immunoglobulin E (IgE), and who responded inadequately or are intolerant to conventional pharmacotherapy. It is available as sublingual tablets of 2,800 bioequivalent allergy unit (BAU). The manufacturer requested listing criteria as per the approved indication.

The manufacturer's submitted price is $3.80 per tablet, or $555 to $897 per year for a grass pollen season of three to six months' duration.

Summary of Economic Analysis

The manufacturer submitted two economic evaluations, a cost-utility analysis (CUA) and a cost-minimization analysis (CMA), from a Canadian health care payer's perspective.[1] The CUA was based on inputs mainly from the literature and, to a lesser extent, on a network meta-analysis and observations from the G8 trial. In addition, in the CUA, the price used for PPAE was outdated ($3.20 per tablet). It compared PPAE with symptomatic treatment and five-grass pollen allergen extract (5GPAE) over a five-year time horizon. The CMA was based mainly on inputs from the network meta-analysis, and it estimated the cost differences between PPAE and perennial and seasonal subcutaneous immunotherapy (SCIT), and 5GPAE over a time horizon of three years from a Canadian health care payer's perspective. Costs considered in the CMA included drug acquisition cost, pharmacy fees, physician visits and injection services, pulmonary function test (for SCIT), and lost productivity (from a societal perspective). Both analyses targeted patients who suffered from moderate to severe seasonal allergic rhinitis to grass pollen.

Results of Manufacturer's Analysis

In the base-case CUA, the manufacturer reported that PPAE had an incremental cost-utility ratio of $36,035 per quality-adjusted life-year compared with symptomatic treatment, and an incremental cost-utility ratio of $33,098 per quality-adjusted life-year compared with 5GPAE (based on the PPAE price of $3.20 instead of $3.80 per tablet).

In the base-case CMA, the manufacturer reported that the three-year cost savings with PPAE was $1,391 per patient compared with perennial SCIT, $862 per patient compared with seasonal SCIT, and $756 per patient compared with 5GPAE.

Interpretations and Key Limitations

Several limitations with the CUA were noted:

- **Model structure:** The manufacturer assumed that allergic rhinitis is a predisposing factor leading to allergic asthma, and therefore allergic asthma was included in the model as a health state. Based on feedback from the consulted clinical expert and a cohort study, cited in the manufacturer's submission,[2] this assumption appears invalid. Further, the submitted model did not include health states pertaining to symptom management and resolution; therefore, it was not sensitive to

differences in clinical effectiveness of the compared interventions. The Common Drug Review (CDR) was unable to revise the model structure for reanalyses.

- **Treatment effects:** In the economic model, the manufacturer assumed differences in post-treatment efficacy between PPAE and 5GPAE; however, the manufacturer's network meta-analysis (included in the submission) showed that 5GPAE was associated with numerically better efficacy (in term of symptoms and medication scores), although it did not reach the statistical significance.
- **Comparators:** SCIT was not included as a comparator, despite being included in the network meta-analysis. The results of the network meta-analysis showed that SCIT has numerically better efficacy than PPAE in term of symptoms and medication scores.
- **Prices and cost of treatment:** Prices used in the CUA were inaccurate. The price used for PPAE was $3.20 per tablet instead of $3.80 (as submitted). In addition, the model considered that PPAE would be used for 365 days annually instead of a range from 116 to 236 days annually, depending on pollen season.

With regard to the CMA:

- Cost of treatments. The manufacturer based its analysis on a pollen season of three months and eight weeks of pre-season treatment. In Canada, the pollen season can range from two to six months. CDR noted that the reported cost savings showed a tendency to decrease with longer pollen seasons and longer pre-season treatment; therefore, the base-case analysis from the CMA model underestimated the costs associated with using PPAE for longer treatment duration. Further, the number of injections for the seasonal SCIT was overestimated (16 per year instead of nine per year, as per the consulted clinical expert); therefore, the CMA model inflated the cost saving of PPAE relative to SCIT.

Results of Common Drug Review Analysis

Given the issues identified with the manufacturer's model and the results of the network meta-analysis, CDR then assumed that the post-treatment efficacy of 5GPAE and PPAE was equal, the utilities of the two comparators were equal, and the differences between treatments were reflected in the cost of therapy, which aligned with the results of the CMA.

The reanalysis of the CMA, assuming a pollen season that ranged from two to six months and pre-season treatment with PPAE that ranged from eight to 16 weeks, showed that the total three-year incremental cost of PPAE (per patient) ranged from a cost saving of $1,717 to a cost impact of $245 compared with perennial SCIT, and a cost saving of $97 to a cost impact of $1,864 compared with seasonal SCIT. PPAE was associated with cost savings ranging from $400 to $837 compared with 5GPAE.

Issues for Consideration

- The Canadian Drug Expert Committee issued a positive recommendation in April 2013 that 5GPAE be listed for the seasonal treatment of grass pollen allergic rhinitis at a reduced price.[3] However, at the time the present report was drafted, none of the participating drug plans listed 5GPAE on their formularies. Where 5GPAE is listed in line with the Committee's recommendation, the price of 5GPAE is lower than the price used in this analysis, and as such PPAE may no longer be cost saving compared with 5GPAE.
- Clinical trials have not studied PPAE in patients older than 65 years.
- Analyses were not stratified by severity of allergic rhinitis; however, based on clinical trials, effects for PPAE in patients with severe allergic rhinitis appeared to be less pronounced.

Conclusions

Based on the results of the manufacturer's network meta-analysis, the efficacy of PPAE and SCIT appear similar, while there may be numerical differences compared with 5GPAE (which favour 5GPAE). Based on current list prices, PPAE could result in an incremental cost per patient over three years that ranges from a cost saving of $1,717 to a cost impact of $1,864 compared with SCIT, depending on duration of pre-season treatment with PPAE and the length of pollen season. Cost saving with SCIT is less certain when compared with seasonal SCIT. Compared with 5GPAE, PPAE results in a three-year per-patient cost savings ranging from $400 to $837.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

The objective of the cost-utility analysis (CUA) included in the pharmacoeconomic submission was to assess the cost-effectiveness of *Phleum pratense* allergen extract (PPAE) compared with symptomatic treatment and five-grass pollen allergen extract (5GPAE) for the treatment of grass pollen-induced allergic rhinitis (AR). The pharmacoeconomic submission also included a cost-minimization analysis (CMA); the objective of the CMA was to estimate the economic impact of PPAE compared with other treatments available in Canada for the treatment of AR induced by grass pollen.

1.2 Treatment

The evaluated treatment was PPAE used for three years. Based on the product monograph, PPAE consists of sublingual tablets of standardized allergenic extract, Timothy grass (*Phleum pratense*). The recommended dose is one sublingual tablet (2,800 bioequivalent allergy units [BAU]) daily. The CUA assumed that PPAE would be used on a daily basis for three years; however, the approved indication in Canada is to use it for at least eight weeks pre-grass pollen season and maintain dosing throughout the allergy season. In the CMA, however, PPAE was assumed to be used as per the recommended dose; i.e., 2,800 BAU per day, for a period that can range from 16.5 to 33.7 weeks per year for a grass season that ranges from two to six months. Patients receiving PPAE were assumed to use symptomatic treatment (rescue medication) if they discontinued PPAE before the end of three years of treatment; in this case, they were assumed to use symptomatic medication from the time of their PPAE discontinuation until the end of year five. The manufacturer considered desloratadine, budesonide, salbutamol, and fluticasone as symptomatic (rescue) medications. The amount of symptomatic medications used was based on observations from the G8 trial; however, the model did not account for the rescue medications that might be used during the three-year treatment with PPAE.

1.3 Comparators

The CUA included two comparators: symptomatic treatment alone and treatment with 5GPAE alone. The analysis assumed that 5GPAE would be used pre- and co-seasonally for three years. Patients in the 5GPAE group were assumed to use symptomatic treatment (rescue medication) in two scenarios. In the first, patients finish three years of 5GPAE treatment; they were assumed to use the symptomatic treatment for years four and five. In the second scenario, patients in the 5GPAE group discontinue 5GPAE before the end of three years of treatment, and were then assumed to use symptomatic medication to control AR symptoms from the time of their 5GPAE discontinuation until the end of year five; the manufacturer considered desloratadine, budesonide, salbutamol, and fluticasone as symptomatic medications. The model considered the same symptomatic medications, including their amounts, for the 5GPAE group as the PPAE group. The model did not account for the rescue medications that might be used during the three-year treatment with 5GPAE.

Subcutaneous immunotherapy (SCIT) is another approved therapeutic option for AR; however, this CUA excluded this therapeutic option without providing any justification.

Comparators in the CMA included SCIT and 5GPAE.

1.4 Type of Economic Evaluation

The manufacturer submitted two separate economic evaluations; the primary analysis was a CMA, and the secondary evaluation was a CUA.[1] The decision to conduct either evaluation depends on the comparative efficacy and safety of the included interventions. The manufacturer used a network meta-analysis (NMA) as the basis for comparative clinical information.[1] The NMA compared PPAE with 5GPAE and sublingual immunotherapies (SLIT, including PPAE and 5-GPAE) with SCIT. Results from this NMA showed that there were no statistically significant differences between PPAE and 5GPAE or between SLIT and SCIT in terms of symptom score and medication score (Table 2). The NMA did not report results comparing PPAE with SCIT; these results would have been more informative regarding the comparative efficacy between PPAE and SCIT. Comparative efficacy between PPAE and symptomatic treatment was obtained from the G8 trial.

TABLE 2: NETWORK META-ANALYSIS RESULTS

Outcome	SLIT versus SCIT	PPAE versus 5GPAE
Symptom score; SMD (95% CI)	0.01 (–0.19 to 0.23)[a]	0.141 (–0.076 to 0.371)[b]
Medication score; SMD (95% CI)	0.13 (–0.31 to 0.57)[a]	0.072 (–0.092 to 0.243)[b]

5GPAE = five-grass pollen allergen extract; CI = confidence interval; PPAE = *Phleum pratense* allergen extract (Grastek); SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SMD = standardized mean difference.
[a]Difference numerically favouring SCIT.
[b]Difference numerically favouring 5GPAE.
Source: Manufacturer's pharmacoeconomic submission.[1]

The cost-utility and the cost-minimization analyses were conducted from a Canadian health care payer's perspective. Societal costs were also accounted for in the CUA, but they were reported separately.

1.5 Population

The CUA modelled a cohort of patients who suffered from moderate or severe seasonal AR to grass pollen. The characteristics of this cohort were based on an observational study conducted by the manufacturer, the time and motion study. The study was conducted in 12 sites, six in Canada and six in the US, and included a total of 670 patients. Its main scope was to provide information on patients, resource needs, and costs associated with SCIT.[1]

The CUA assumed that the average age of the initial patients was 27 years old, and 23.7% of patients initiating immunotherapy had co-existing allergic asthma. However, the time and motion study reported that the average age of the included patients was 44 years in Canada and 41 years in the US, and it reported that about 24% and 43% of patients had asthma in Canada and the US, respectively. These discrepancies between the modelled cohort and the observational study were not explained or justified in the submitted economic evaluation.

The target population considered in the CMA consisted of adults and children five years of age and older who have AR confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense*–specific immunoglobulin E, and who have responded inadequately or are intolerant to conventional pharmacotherapy.

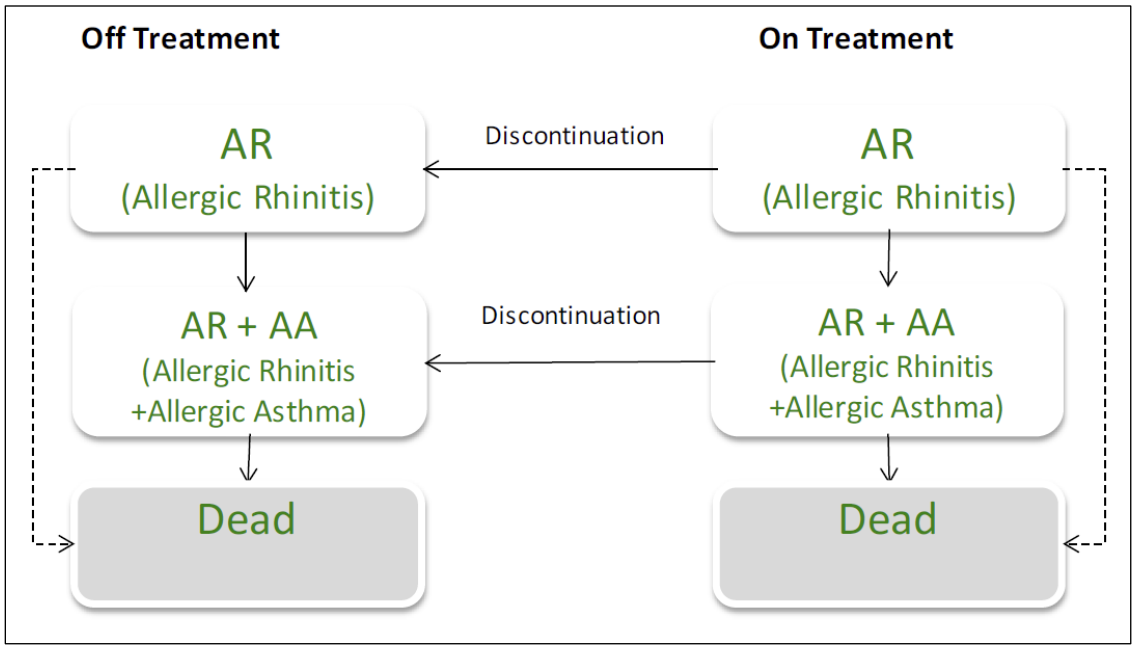
2. METHODS

Please see Table 10 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure for the Cost-Utility Analysis

The submitted model included three health states: AR, AR and allergic asthma, and death. Patients simulated in the model could be in any of these states while on treatment or off treatment. The model allowed for three transitions: progression to allergic asthma, discontinuation of the treatment, and death. Figure 1 below summarizes the transitions between the three health states. The Common Drug Review (CDR) identified several limitations concerning the submitted model that might compromise the interpretability of its results. First, the model assumed that AR predisposes patients to allergic asthma; however, the consulted clinical expert confirmed that AR is not a risk factor for allergic asthma. Second, the proposed model did not capture outcomes specific to AR, such as presence or absence of symptoms and their severity; this limitation made the model insensitive to differences between the compared therapeutic options.

FIGURE 1: THE COST-UTILITY MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[1]

2.2 Clinical Inputs

2.2.1 Efficacy

The CUA did not include explicit efficacy variables. The studies included in the clinical CDR report evaluated two efficacy measures: the symptom score and medication score. Comparative efficacy between PPAE and symptomatic treatment was based on the G8 trial. The model assumed equal therapeutic efficacy for PPAE and 5GPAE during the three-year period of treatment, based on the NMA results. However, the CUA model assumed that patients treated with PPAE for three years would have an extended efficacy for two additional years, based on observations from the G8 trial, while patients

treated with 5GPAE would not have any extended efficacy beyond the three years of treatment, based on absence of published evidence of its long-term efficacy.

The comparative efficacy between PPAE versus 5GPAE and symptomatic treatment did not affect the transition probabilities in the submitted model; however, it was used to justify the differences in utility values (2.2.6 Utility Values for Allergic Rhinitis and Allergic Asthma).

2.2.2 Harms

Measures for harm were not included in the CUA model. However, the clinical review reported that PPAE, compared with symptomatic treatment, was associated with higher incidence of ear, eye, and mouth pruritus; mouth edema; throat irritation; and nasopharyngitis. The submitted model did not consider the cost impact of these adverse events.

2.2.3 Disease Progression

The model considered two progressive states for AR: allergic asthma and death. The model considered an annual rate of 0.46% for the progression for AR to allergic asthma; the same annual probability of progression was applied for three comparators.

The probability of progression to allergic asthma was based on a longitudinal cohort;[2] the cohort reported an unadjusted 8.8-year cumulative probability rate of 3.8% (0.44% annual probability) of developing allergic asthma in AR patients compared with patients who do not have AR. However, the submitted model used an unadjusted risk probability of developing allergic asthma in AR patients; the same study reported that when this risk was adjusted for baseline and follow-up values of bronchial hyperresponsiveness, the relative risk of asthma decreased from 3.53 (95% CI, 2.11 to 5.91) to 1.90 (0.91 to 3.95). These results further challenged the model assumption that AR predisposes individuals to allergic asthma, while in fact the association between the two diseases could be explained by common risk confounders.

2.2.4 Treatment Discontinuation Rate

The model adopted the literature-based discontinuation rate reported on general sublingual immunotherapy compounds.[4] The discontinuation rates used were 29% in the first year, 28% in the second year, and 0% in third year for both PPAE and 5GPAE. The applied discontinuation rates did not provide additional information on the comparative CUA of PPAE or 5GPAE, and their inclusion in the model was not justified.

2.2.5 Mortality

The model adopted a mortality rate for patients with AR equal to the all-cause mortality rate for the general Canadian population. Mortality rate for patients with allergic asthma was based on a 16-year cohort study of 31,110 Finnish adults.[5] The study reported that patients with allergic asthma had a mortality hazard ratio of 1.49 compared with non-asthmatic population.[5] The above mortality rates were applied equally for the three interventions: PPAE, 5GPAE, and symptomatic treatment. These mortality rates did not provide additional information on the comparative CUA of PPAE, 5GPAE, or symptomatic treatment, because the model used equal progression rates for the three comparators and the model's outcomes did not rely on patients' survival.

2.2.6 Utility Values for Allergic Rhinitis and Allergic Asthma

The model adopted utility values based on EQ-5D values observed in the GT-08 trial. Patients receiving PPAE reported utility scores of 0.9626 for AR and 0.9391 for co-existing allergic asthma.[6,7] The

manufacturer applied these utilities for both the PPAE and 5GPAE groups for year one to year three if patients were receiving PPAE or 5GPAE. However, if patients discontinued before year three, the manufacturer assumed that patients lost treatment effects and their mean utility would be the same as the symptomatic treatment group, which were 0.9459 for patients with AR and 0.9141 for patients with co-existing allergic asthma.[6,7]

Another assumption was that patients on PPAE sustained their utility score for five years, as long as they finished three years of PPAE; however, patients on 5GPAE sustained their utility score for only three years, and symptomatic treatment utilities were used for the fourth and fifth years for patients on 5GPAE (Table 3). The reported reason for the assumption of differential sustainability of utility scores was that the GT-08 trial reported five-year results showing that PPAE sustained its efficacy for an extra two years after three years of treatment, while there is no published evidence that shows efficacy is sustained for 5GPAE beyond three years.

TABLE 3: QUALITY OF LIFE UTILITIES

	Allergic Rhinitis	Allergic Rhinitis + Allergic Asthma
Symptomatic Treatment	0.9459	0.9141
PPAE		
On or completed treatment (years one to five)	0.9626	0.9391
Early discontinuation	0.9459	0.9141
5GPAE		
On or completed treatment (years one to three)	0.9626	0.9391
Completed treatment (years four and five)	0.9459	0.9141
Early discontinuation	0.9459	0.9141

5GPAE = five-grass pollen allergen extract; PPAE = *Phleum pratense* allergen extract.
Source: Manufacturer's pharmacoeconomic submission.[1]

2.2.7 Costs

a) Drug Costs

The model assumed that PPAE would be taken as one tablet per day for three years. 5GPAE would be taken as one tablet per day for four months per season and three months co-season for three years (Table 4). According to the clinical expert consulted for this review, there is a considerable regional variation in length of allergy season in Canada, but the clinical expert considered a three-month period to be a reasonable average of this variation.

TABLE 4: DRUG USE AND COST

	Drug Use/Year[a] Tablets	Cost per Tablet	Annual Drug Cost
Symptomatic Treatment	0	$0	$0
PPAE	365[b]	$3.20[c]	$1,168
5GPAE	210[d]	$1.26 (100 IR dose)[e,f] $3.80 (300 IR dose)[e,f]	$798

5GPAE = five-grass pollen allergen extract; IR = index of reactivity; PPAE = *Phleum pratense* allergen extract.
[a]From year one to year three.
[b]The model assumed that PPAE is used daily for three years; however, the approved indication is for PPAE to be used at least eight weeks per season and with dosing maintained throughout the season. This means that PPAE is to be used for 146 days (three-month allergy season).
[c]The model used a price of $3.2/ tablet of PPAE; however, the submitted price is $3.80/ tablet.
[d]Based on a three-month allergy season.
[e]100 IR per day is a titration dose used in the first two days as one dose on day one and two doses on day two; the maintenance dose is 300 IR per day.
[f]The model used a 5GPAE price based on IMS Brogan Delta PA, wholesaler, Ontario, September 2013. However, a more recent (January 2014) price based on McKesson Canada wholesale pricing showed higher prices for 5GPAE ($1.37 and $4.123 for the 100 IR and 300 IR doses, respectively).

b) Administration Costs

Administration costs included in the model were dispensing fee, physician start-up visit, and physician follow-up visits. The model considered 90-day dispensing for PPAE and 5GPAE; although some patients may be eligible for the 90-day dispensing, this may not be generalizable for the majority of patients. Both PPAE and 5GPAE should be initiated under medical supervision; the model accounted for one physician start-up visit, at year one, for PPAE, and for a total of three visits for 5GPAE, one visit per year. This differential application of start-up visits is in line with the product monograph recommendation that 5GPAE should be administered under medical supervision whenever the dose is interrupted for more than a week. The model considered one follow-up visit per year for PPAE and 5GPAE and two visits per year for patients on symptomatic treatment (Table 5).

TABLE 5: ADMINISTRATION RESOURCES AND COSTS (LITERATURE-BASED)

	Start-up Visits/ Year	Cost/Start-up Visit	Follow-up Visits/Year		Cost/Follow-up Visit
			AR	AA+AR	
Symptomatic treatment	0	NA	2	2.4	$61.25
PPAE	1[a]	$38.05	1	1	$61.25
5GPAE	1[b]	$38.05	1	1	$61.25

5GPAE = five-grass pollen allergen extract; AA = allergic asthma; AR = allergic rhinitis; NA = not applicable; PPAE = *Phleum pratense* allergen extract.
[a]Occur in year one only.
[b]Occur each year.
Source: Manufacturer's pharmacoeconomic submission.[1]

c) Rescue Medication Costs

The model based estimates for rescue medication on the GT-08 trial. It included the use of desloratadine and budesonide for patients with AR, and it included salbutamol and fluticasone for patients who have allergic asthma on top of their AR. The trial estimates were applied directly in the model for PPAE and symptomatic treatment groups. It was assumed in the model that patients on 5GPAE would have the same recourse to rescue medication as for PPAE in the first three years; for years four and five, it was

assumed that patients on 5GPAE would have rescue medication use similar to symptomatic treatment (Table 6). The model accounted for the use and costs of desloratadine within the societal perspective only because desloratadine is an over-the-counter medication.

TABLE 6: ANNUAL USE AND COSTS OF RESCUE MEDICATIONS (TRIAL-BASED)

	Symptomatic Treatment (Years 1 to 5)	PPAE (Years 1 to 5)	5GPAE	
			Years 1 to 3	Years 4 and 5
Desloratadine, 5 mg[a]				
Tablets used by AR	13.13	9.69	9.69	13.13
Tablets used by AR+AA	15.88	13.22	13.22	15.88
Cost/tablet	$0.83			
Budesonide, 32 mcg				
Puffs used by AR	20.12	11.60	11.60	20.12
Puffs used by AR+AA	22.43	15.68	15.68	22.43
Cost/puff	$0.04			
Salbutamol, 200 mcg				
Inhalations used by AR	2.08	2.26	2.26	2.08
Inhalations used by AR+AA	9.43	9.08	9.08	9.43
Cost/inhalation	$0.69			
Fluticasone, 250 mcg				
Inhalations used by AR	1.68	0.64	0.64	1.68
Inhalations used by AR+AA	8.29	3.77	3.77	8.29
Cost/inhalation	$0.69			

5GPAE = five-grass pollen allergen extract; AA = allergic asthma; AR = allergic rhinitis; NA = not applicable; PPAE = *Phleum pratense* allergen extract.
[a]Desloratadine is a non-prescription medication, and it was included in the societal perspective analysis only.
Source: Manufacturer's pharmacoeconomic submission.[1]

d) Productivity Loss

The societal perspective analysis included the amount of time missed from work, as captured in the GT-08 trial for patients on PPAE and symptomatic treatment. For patients on 5GPAE, the model assumed that they would have the same missed time as for patients on PPAE in the first three years; for years four and five, the model assumed that they would have missed time similar to patients on symptomatic treatment (Table 7).

TABLE 7: PRODUCTIVITY LOSS (TRIAL-BASED)

	Symptomatic Treatment (Years 1 to 5)	PPAE (Years 1 to 5)	5GPAE	
			Years 1 to 3	Years 4 and 5
Hours missed from work				
Hours lost by AR	2.81	0.45	0.45	2.81
Hours lost by AR+AA	6.27	2.12	2.12	6.27
Cost/tablet	$24.01			

5GPAE = five-grass pollen allergen extract; AA = allergic asthma; AR = allergic rhinitis; PPAE = *Phleum pratense* allergen extract.
Source: Manufacturer's pharmacoeconomic submission.[1]

2.2.8 Time Horizon

The model considered a five-year time horizon in the base-case analysis, based on observations from the GT-08 trial. The GT-08 trial showed that three-year treatment with PPAE provided a sustained efficacy of PPAE of a further two years. In the sensitivity analysis, the model considered a 10-year time horizon. The cycle length in the submitted model was one year and half-cycle correction was applied. For patients who discontinued treatment before the end of the full cycle, the model retained half of the treatment benefits and half of the costs for that year.

2.2.9 Discounting

The model applied a 5% annual discount rate for costs and outcomes.

2.2.10 Sensitivity Analyses

The model included several one-way sensitivity analyses on the discount rate (rage from 0% to 5%), length of allergy season (range from two to six months), 5GPAE effect (assuming sustained effect for a further year after three-year treatment), and on time horizon (assuming 10 years of time horizon). In addition to the one-way sensitivity analysis, a probabilistic sensitivity analysis was conducted to reflect uncertainty regarding transition probabilities, utilities, and resource use; the probabilistic sensitivity analysis was not applied on unit costs.

3. RESULTS

3.1 Manufacturer's Base Case

The base-case results showed that the incremental cost-utility (ICUR) of PPAE was $36,035 per quality-adjusted life-year (QALY) compared with symptomatic treatment, and $33,098 per QALY compared with 5GPAE (Table 8). However, the base-case analysis used inaccurate prices for PPAE and 5GPAE and an inaccurate dosing regimen for PPAE. First, the model used a PPAE price of $3.20 per tablet instead of $3.80 per tablet, and it used 5GPAE prices of $1.26 and $3.80 instead of $1.37 and $4.123 for the 100 and 300 index of reactivity (IR) doses, respectively. Second, the inaccuracy was in the dosing regimen, which assumed that PPAE was used for 365 days per year instead of 146 days per year (accounting for a three-month pollen season).

TABLE 8: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of PPAE ($)	Total QALYs	Incremental QALYs of PPAE	Incremental Cost per QALY
PPAE	2,461[a]		4.3103		
Symptomatic treatment	599	1,862	4.2586	0.0517	36,035
5GPAE	1,926[b]	535	4.2941	0.0162	33,098

5GPAE = five-grass pollen allergen extract; IR = index of reactivity; PPAE = *Phleum pratense* allergen extract; QALY = quality-adjusted life-year.
[a]Costs were based on PPAE price of $3.20/tablet instead of $3.80/tablet.
[b]Costs were based on 5GPAE prices of $1.26 and $3.80 instead of $1.37 and $4.123 for the 100 IR and 300 IR doses, respectively.
Source: Manufacturer's pharmacoeconomic submission.[1]

When the societal perspective was considered in the analysis, the ICUR for PPAE dropped to $31,781 per QALY compared with symptomatic treatment and $28,828 per QALY compared with 5GPAE.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-way Sensitivity Analyses

The length of allergy season and sustainability of 5GPAE effect were key drivers of the model. 5GPAE administration was based on the length of the allergy season, while PPAE was considered to be administered all year round; therefore, shorter allergy seasons of two months would result in an ICUR of PPAE equal to $45,754 per QALY compared with 5-GPAE. On the other hand, a longer allergy season of six months resulted in PPAE dominating 5GPAE (more effective, less costly). However, this analysis was not accurate because the administration of both PPAE and 5GPAE depend on the length of allergy season, and this would offset the differences between the two interventions.

With regard to 5GPAE efficacy beyond the three-year treatment, the ICUR was very sensitive when one additional year of efficacy was attributed to 5GPAE; the corresponding ICUR of PPAE was $71,676 per QALY.

3.2.2 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis showed that for a willingness-to-pay threshold of $50,000 per QALY, there was a 99.85% chance that this submitted analysis would produce results showing PPAE would be

cost-effective compared with symptomatic treatment alone, and a 99.93% chance that PPAE would be cost-effective compared with 5GPAE.

3.3 Common Drug Review Analyses

CDR analyses were conducted to correct the inaccuracy in price and length of administration used for PPAE. The corrected values were then used to rerun the manufacturer's base-case analysis and two sensitivity analyses, length of allergy season, and sustainability of 5GPAE effect. CDR also tested the hypothesis of equal sustained efficacy for PPAE and 5GPAE for two years post treatment.

Price and regimen corrections reduced the total cost of PPAE by 43.3% of the initial cost used in the model, and this affected the cost-effectiveness results compared with 5GPAE and the symptomatic treatment. The ICUR of PPAE became $15,411 compared with the symptomatic treatment, and PPAE became dominant relative to 5GPAE (Table 9).

CDR tested the hypothesis of equal sustained efficacy of 5GPAE and PPAE for two years post treatment. The results showed that both interventions would have the same utility values; therefore, the difference between them was due to their respective prices only.

TABLE 9: SUMMARY OF RESULTS OF COMMON DRUG REVIEW ANALYSIS

	Total Costs ($)	Incremental Cost of PPAE ($)	Total QALYs	Incremental QALYs of PPAE	Incremental Cost per QALY of PPAE
Base-case analysis[a,b]					
PPAE	1,395[c]		4.3103		
Symptomatic treatment	599	796	4.2587	0.0517	15,414
5GPAE	2,025	-630	4.2942	0.0162	PPAE dominates
Allergy season of 2 months[b]					
PPAE	1,205[c]		4.3103		
Symptomatic treatment	599	606	4.2587	0.0517	11,732
5GPAE	1,819	–614	4.2942	0.0162	PPAE dominates
Allergy season of 6 months,[b] and 16-week pre-season treatment with PPAE					
PPAE	2,349		4.3103		
Symptomatic treatment	599	1,750	4.2587	0.0517	33,872
5GPAE	2,673	–324	4.2941	0.0162	PPAE dominates
Sustained efficacy of 5GPAE for 1 year post treatment[b]					
PPAE	1,395[c]		4.3103		
Symptomatic treatment	599	796	4.2587	0.0517	15,411
5GPAE	1,995	–600	4.3024	0.0079	PPAE dominates
Sustained efficacy of 5GPAE for 2 years post treatment[b]					
PPAE	1,395[c]		4.3103		
Symptomatic treatment	599	796	4.2587	0.0517	15,411
5GPAE	2,025	–630	4.3103	0	NA

5GPAE = five-grass pollen allergen extract; NA = not applicable; PPAE = *Phleum pratense* allergen extract; QALY = quality-adjusted life-year.

[a]Assuming 3-month allergy season.

[b]Based on corrected price for PPAE and 5-GPAE, corrected regimen for PPAE, and 3 dispensing fees for 5GPAE instead of 4.

[c]Based on 8-week pre-season treatment; however, the clinical trials treated patients with PPAE for 8 to 16 weeks pre-seasonal. Using PPAE for longer than 8 weeks pre-seasonal would increase its cost estimates.

4. DISCUSSION

The submitted CUA estimated the incremental cost-effectiveness ratios of PPAE in comparison with 5GPAE and symptomatic treatment. The analysis had several limitations, summarized in Table 10. One of these was that the submitted model assumed that AR is a predisposing factor leading to allergic asthma, and therefore allergic asthma was included in the model as a health state; however, the consulted clinical expert and a cohort study cited in the manufacturer's submission invalidated this assumption. In fact, the manufacturer used the cohort study to estimate the probability of progression of AR to allergic asthma.[4] The result of the cohort study reported an unadjusted relative risk of 3.53 (95% CI, 2.11 to 5.91) of developing allergic asthma in AR patients compared with those without AR, which shows a statistically significant association between AR and allergic asthma. However, the same cohort reported that when this risk was adjusted for baseline and follow-up values of bronchial hyperresponsiveness, the relative risk of asthma decreased from 3.53 (95% CI, 2.11 to 5.91) to 1.90 (0.91 to 3.95). The adjusted analysis further challenges the model assumption that AR predisposes patients to allergic asthma, while in fact the association between the two diseases could be explained by common risk confounders. Another flaw in the submitted model was that it did not include health states pertaining to symptom management and resolution; therefore, it was not sensitive to differences in clinical effectiveness of the compared interventions. Another limitation was that the model excluded SCIT from the comparators, despite an NMA submitted by the manufacturer showing that SCIT has numerically better efficacy than PPAE.

TABLE 10: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/ Assumption	Issue	Impact
Model structure	It did not include a health state for remission (patients with no allergic rhinitis)	Could not be evaluated
	It assumed that allergic rhinitis predisposes patients to allergic asthma; the consulted clinical expert confirmed that allergic rhinitis is not a risk factor for allergic asthma	
	It considered "treatment discontinuation" to be a separate health state, but it did not differentiate between discontinuation due to inefficacy or intolerance and discontinuation due to remission	
Inaccurate dosing and pricing	The model assumed that PPAE is used for 365 days/year, while the approved indication is for at least 8 weeks per season with dosing maintained throughout the season. The model used $3.20, $1.26, and $3.80 as the price per tablet of Grastek, 5GPAE 100 IR, and 5GPAE 300 IR, respectively	Overestimated the price difference in favour of 5GPAE. CDR estimate of the annual drug cost difference is a cost saving of $307 instead of a cost of $525 (for 3-month allergy season)
	Might overestimate the cost of rescue medication for patients on 5GPAE	Overestimated the price of rescue medication used by patients on 5GPAE in years 4 and 5. CDR estimate of the annual rescue medication cost in years 4 and 5 for 5GPAE group is $4.90 instead of $9.50
Assuming that 5GPAE efficacy not sustained after 3-year treatment	Might underestimate the quality of life utility for patients on 5GPAE in years 4 and 5	Overestimated cost-effectiveness of PPAE. CDR assumed equal effect sustainability for PPAE and 5GPAE: ICUR could not be calculated due to equal utilities; however, the difference between the two groups became a cost difference only

5GPAE = five-grass pollen allergen extract; CDR = Common Drug Review; ICUR = incremental cost-utility ratio; IR = index of reactivity; PPAE = *Phleum pratense* allergen extract.

Another major limitation of the submitted CUA was the assumption that 5GPAE would not sustain its efficacy beyond the treatment period. In fact, the inputs used in this analysis were based on GT-08 trial results comparing PPAE with symptomatic treatment. The results showed that PPAE improved disease symptom scores and medication scores during the three-year treatment period, and this efficacy was sustained for a further two years. Comparison between PPAE, SCIT, and 5GPAE was based on an NMA submitted by the manufacturer and showed that SCIT and 5GPAE were numerically better than PPAE in terms of symptom score or medication score. However, the NMA provided information limited to the three-year treatment period, but there was a gap in evidence relative to the post-treatment efficacy. This lack of information was used in the economic evaluation as a basis of the main assumption that 5GPAE would not sustain its efficacy after treatment termination. However, the lack of information provides a source of uncertainty about the comparative efficacy between 5GPAE and PPAE after the termination of treatment. The model base case assumed the extreme case that 5GPAE would not have

any sustained efficacy, but did not consider an assumption that 5GPAE would sustain its full efficacy in a similar manner to PPAE.

Given the above limitations, especially with regard to the assumed effect benefit for PPAE compared with 5GPAE, a CUA may not be the most appropriate method for conducting this evaluation.

In parallel with the CUA, the manufacturer submitted a CMA that compared PPAE with SCIT administered perennially and seasonally, versus 5GPAE. The CMA might be a suitable alternative for the submitted CUA because it included SCIT, and it did not assume a differential post-treatment efficacy between PPAE and 5GPAE. Therefore, CDR's conclusions would be based mainly on the CMA.

The CMA was conducted from the perspective of the public payer, over a three-year time horizon. The comparative effectiveness assumption required for the use of a CMA was supported by the NMA provided by the manufacturer, which is further discussed in the supplemental issue of this report; its main results were provided in Table 2.[1] Costs considered included drug acquisition cost, pharmacy fees, physician visits and injection services, pulmonary function test (for SCIT), and lost productivity (from societal perspective).

The manufacturer reported cost savings from the public payer perspective. For the first year of therapy, the total health care costs were $671 for PPAE, $1,773 for perennial SCIT, $948 for seasonal SCIT, and $936 for 5GPAE, resulting in a cost savings for PPAE of $1,102 when compared with perennial SCIT, $277 compared with seasonal SCIT, and $431 compared with 5GPAE. While drug costs were greater for PPAE ($575, compared with $290 for perennial SCIT and $208 for seasonal SCIT), other costs, such as physician costs and cost for pulmonary function tests, were lower for PPAE ($99) compared with perennial SCIT ($1,484) and seasonal SCIT ($741). For subsequent years, the health care costs of the four comparators were stabilized (PPAE $633, and perennial SCIT $789, seasonal SCIT $948, and 5GPAE $898).

The following limitations with the manufacturer's CMA were noted:

Drug Cost

- The drug costs used for 5GPAE were outdated, and a more recent price is available. The model used $1.26 and $3.80 instead of $1.37 and $4.12 for the 100 IR and 300 IR doses, respectively.
- The drug cost of PPAE was based on a three-month pollen season and eight-week pre-season treatment. However, grass pollination is reported to peak between three and six months in duration depending on the specific allergen.[8] Moreover, the product monograph indicates that PPAE should be taken throughout the pollen season, which could potentially extend further than the peak durations. Furthermore, the product monograph indicates that PPAE may be used for more than eight weeks pre-season, without specifying a maximum duration.[9] Although the clinical review included clinical studies in which the pre-season treatment with PPAE ranged from 8 to 16 weeks, the consulted clinical expert confirmed that PPAE would probably be prescribed only for eight weeks pre-season. Use of PPAE for a prolonged period would increase its incremental cost beyond what was reported by the manufacturer. The drug acquisition cost for PPAE is expected to vary between $458 and $1,144, depending on the duration of the pre-season and the pollen season (8 to 16 weeks pre-season and a two to six-month pollen season). The dosing frequency of seasonal SCIT was higher in the economic analysis (weekly for three months pre-season and monthly during the pollen season, for a total of 16 injections) than the nine weekly injections pre-season dosing described by the CDR clinical expert consulted. This would decrease the anticipated cost savings for drug plans that reimburse SCIT.

- In the patients' costs, the model accounted for a total of 56 and 45 physician visits for "efficacy assessment of injection" for the perennial and seasonal SCIT, respectively. However, patients who are treated with SCIT usually see their physician very frequently to receive the injections, and there is no need for separate visits for efficacy assessment. Removing these visits will reduce the expected cost savings from PPAE.

In order to account for these limitations, CDR considered a revised scenario assuming reduced frequency of administration of seasonal SCIT (nine injections), potentially longer allergy season with PPAE (two versus six months), potentially longer pre-season treatment with PPAE, and removing the costs generated by the "efficacy assessment" visits from patients' costs. The total three-year incremental cost (per patient) of PPAE (8 versus 16 weeks pre-season treatment with PPAE and two- versus six-month pollen season) ranged from a cost savings of $1,717 to a cost impact of $245 compared with perennial SCIT, and a cost saving of $97 to a cost impact of $1,864 compared with seasonal SCIT, and a cost saving ranging from $837 to $400 compared with 5GPAE. Table 11 summarizes the potential impact of treatment duration with PPAE when compared with SCIT and 5GPAE.

TABLE 11: SUMMARY OF RESULTS OF COMMON DRUG REVIEW COST-MINIMIZATION ANALYSIS

Pollen Season (Months)	PPAE Pre-treatment Duration (Weeks)	Total Health Care Cost Associated With PPAE	Incremental Cost Saving (Impact)[a] Versus		
			Perennial SCIT	Seasonal SCIT	5GPAE
2	**8**	$1,523	$1,717	$97	$898
2	**10**	$1,675	$1,565	**($55)**	$594
2	**16**	$2,131	$1,109	**($511)**	$290
3	**8**	$1,849	$1,391	**($229)**	$950
3	**12**	$2,153	$1,087	**($533)**	$646
3	**16**	$2,482	$758	**($862)**	$317
4	**8**	$2,175	$1,065	**($555)**	$978
4	**12**	$2,504	$736	**($883)**	$649
4	**16**	$2,808	$432	**($1,188)**	$345
5	**8**	$2,525	$714	**($905)**	$981
5	**12**	$2,830	$410	**($1,209)**	$677
5	**16**	$3,134	$106	**($1,514)**	$373
6	**8**	$2,851	$388	**($1,231)**	$1,034
6	**13**	$3,256	**($16)**	**($1,636)**	$729
6	**16**	$3,485	**($245)**	**($1,864)**	$400

5GPAE = five-grass pollen allergen extract; PPAE = *Phleum pratense* allergen extract; SCIT = subcutaneous immunotherapy.
[a]Analysis was based on 9 injections of seasonal SCIT and removing the costs generated by the "efficacy assessment" visits from patients' costs.

Patient Input

The Asthma Society of Canada is a national charitable volunteer-supported organization that collected information for this submission through an online survey, focus group, and one-on-one interviews. A substantial proportion of respondents were diagnosed with allergies to grass pollen and other seasonal allergies, although less than a third of these patients were diagnosed with a specific allergy to Timothy grass.

Patients reported the following:

- Their principal concern is living with the daily or weekly threat of severe asthma exacerbations that may be triggered by seasonal allergy. Commonly reported symptoms — such as shortness of breath, wheezing, sinus congestion, poor or disrupted sleep and resultant fatigue, loss of sense of taste and smell, tightness in the chest, skin rashes, persistent cough and depression — were reported to adversely affect a person's work, social, and home life.
- The patient group reported that the disease has a significant impact on caregivers as well.
- Current therapies are reasonably effective, but the pharmaceutical therapies often have moderate to severe side effects and may become less effective for patients on a long-term basis. Respondents identified a desire for new medications to maintain control of their illness, which reduce side effects such as blocked nasal passages, asthma attacks, cough, fatigue, mood swings, and headache. Respondents also indicated that they would appreciate an oral treatment to take at home.

The manufacturer's primary analysis (CMA) does not consider any of the areas of interest or concern outlined by the patient group. While some of these effects may have been inherently captured in utility values in the submitted CUA, these values were not sourced from PPAE trials, and thus may not be representative.

Issues for Consideration

The Canadian Drug Expert Committee issued a positive recommendation in April 2013 that 5GPAE be listed for the seasonal treatment of grass pollen AR at a reduced price.[3] However, at the time the present report was drafted, none of the participating drug plans had listed 5GPAE on their formularies. If 5GPAE were to be listed in line with the Canadian Drug Expert Committee (CDEC) recommendation, the price of 5GPAE would likely be lower than the price used in this analysis. If this was the case, PPAE might no longer be cost saving compared with 5-GPAE.

The generalizability of the economic review might be compromised by the limited clinical evidence. For example, PPAE is indicated for use by pediatric and adult patients; however, pediatric population was not considered in the CUA, and the CMA did not report results specific for this subgroup. Therefore, the cost-effectiveness of PPAE in pediatric patients is unknown. Another gap in evidence was that the efficacy of PPAE was not evaluated in patients older than 65 years, and this would limit the validity of the economic evaluation to patients of this age group, which comprises a large proportion of patients covered under the public drug plans. Finally, the clinical report showed that PPAE might be less effective when used in more severe patients; however, the economic review did not include subgroup analysis specific to disease severity at baseline, and thus the cost-effectiveness of PPAE in severe AR could not be verified.

The Scottish Medicines Consortium, Scotland's health technology assessment agency, has on three separate occasions provided a negative recommendation for Grastek for the treatment for grass pollen-induced AR with or without conjunctivitis, with clinically relevant symptoms and a positive skin prick test and/or a specific immunoglobulin E test to grass pollen. The decision was based mainly on economic considerations in April and December 2004, and it was based on the absence of a submission for an extension to the indication from the holder of the marketing authorization. Summaries of these recommendations are provided in Appendix 4: Other Health Technology Assessment Findings.

5. CONCLUSIONS

Based on the results of the manufacturer's network meta-analysis, the efficacy of PPAE and SCIT appear similar, while there may be numerical differences compared with 5GPAE (which favour 5GPAE). Based on current list prices, PPAE could result in an incremental cost per patient over three years that ranges from a cost saving of $1,717 to a cost impact of $1,864 compared with SCIT, depending on the duration of pre-season treatment with PPAE and the length of the pollen season. Cost savings with SCIT are less certain when compared with seasonal SCIT. Compared with 5GPAE, PPAE results in a three-year per patient cost savings ranging from $400 to $837.

APPENDIX 1: COST COMPARISON TABLE FOR MEDICATIONS USED FOR THE TREATMENT OF ALLERGIC RHINITIS

The comparator treatments presented in the table below have been deemed the appropriate comparators by clinical experts. Costs are manufacturer list prices, unless otherwise specified.

TABLE 12: ORAL AND INJECTABLE AGENTS INDICATED FOR ALLERGIC RHINITIS

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)	Recommended Treatment Regimen	Complete Treatment Duration	Average Cost per Treatment Regimen ($)
PPAE	**2,800 BAU**	**SL tab**	**3.8000[a]**	**One tablet daily** **Initiate dosing at least 8 weeks before grass pollen season and maintain throughout season**	Up to 3 years	**555 to 897[b]**
5GPAE[c]	100 IR 300 IR	SL tab SL tab	1.3700[d] 4.1230[d]	Initiation: Day 1: 1 x 100 IR Day 2: 2 x 100 IR Day 3: 1 x 300 IR Maintenance: 300 IR once daily for 4 months pre-pollen season & maintain throughout season	Up to 3 years	862 to 1,233[b]
GPAE, seasonal treatment	100,000 BAU/mL, diluted according to patient reactivity	Glycerinated solution for SC injection	17.7240[e] per mL for orchard grass	9 weekly injections pre-pollen season	3 to 5 years	80[f]
GPAE, annual treatment	100,000 BAU/mL, diluted according to patient reactivity	Glycerinated solution for SC injection	17.7240[e] per mL for orchard grass	Initiation: Weekly injections for 5 to 8 months Maintenance: Monthly injections	3 to 5 years	Year 1: 248 to 346[f] Subsequent years: 106[f]

5GPAE = five-grass pollen allergen extract; BAU = bioequivalent allergy unit; GPAE = grass pollen allergen extract; IR = index of reactivity; PPAE = *Phleum pratense* allergen extract; SCIT = subcutaneous immunotherapy; SC = subcutaneous; SL = sublingual.

[a]Manufacturer's submitted price.

[b]Assumes a grass pollen season of 3 to 6 months' duration.

[c]Consists of 5 distinct grass pollens, namely cocksfoot (*Dactylis glomerata* L.), sweet vernal grass (*Anthoxanthum odoratum* L.), rye grass (*Lolium perenne* L.), meadow grass (*Poa pratensis* L.), and Timothy grass (*Phleum pratense* L.).

[d]McKesson Canada wholesale pricing (accessed Jan 2014).

[e]Source: Non-insured Health Benefits (Feb 2014); based on maximum volume of injection of 0.5 mL.

[f]Assumes a dose of 0.5 mL per injection, 21 weekly injections, and 7 monthly maintenance injections.

Although not deemed appropriate comparators by clinical experts, these drugs are used as first-line treatments for allergic rhinitis. Some of these drugs have explicit indications for AR, but not specific to grass pollen.

TABLE 13: OTHER PRESCRIPTION MEDICATIONS FOR ALLERGIC RHINITIS

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)	Usual Dose	Daily Cost ($)	Average Annual Cost[a] ($)
Nasal Sprays						
Beclomethasone (Gen-Beclo AQ)	50 mcg/ spray 200 doses	Nasal spray	12.2600	2 sprays/nostril twice daily	0.49	179
Budesonide (Rhinocort Turbuhaler)	100 mcg/ spray 200 doses	Nasal spray	24.1500	2 sprays/nostril once daily	0.48	176
Budesonide (Rhinocort Aqua)	64 mcg/ spray 120 doses	Nasal spray	10.9000	2 sprays/nostril once daily	0.36	133
Budesonide (Gen-Budesonide AQ)	100 mcg/ spray 165 doses	Nasal spray	12.7400	2 sprays/nostril once daily	0.31	113
Ciclesonide (Omnaris)	50 mcg/ spray 120 doses	Nasal spray	25.7800	2 sprays/nostril once daily	0.86	314
Fluticasone propionate[b] (generics)	50 mcg/ spray 120 doses	Nasal spray	21.9700[c]	2 sprays/nostril once daily	0.73	267
Mometasone[b] (Nasonex)	50 mcg/ spray 140 doses	Nasal spray	29.6700[c]	2 sprays/nostril once daily	0.85	309
Triamcinolone acetonide[b,c] (Nasacort AQ)	55 mcg/ spray 120 doses	Nasal spray	24.0000	2 sprays/nostril once daily	0.80	292
Prescription-Strength Antihistamines						
Cetirizine[b] (generics)	20 mg	Tab	0.7535[d]	½ to one tablet daily	0.38 to 0.75	138 to 275
Leukotriene Receptor Antagonists						
Montelukast[b] (generics)	4 mg 4 mg 5 mg 10 mg	Chew tab Oral gran Chew tab Tab	0.5044[c] 0.5833[c] 0.5565[c] 0.8195[c]	10 mg daily	0.82	299

[a]Assumes year-round use.
[b]Drug has explicit indication for allergic rhinitis, but not specific due to grass pollen.
[c]Saskatchewan Formulary (Jan 2014).
[d]McKesson Canada wholesale price (Jan 2014).
Source: Ontario Drug Benefit Formulary (Jan 2014) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 14: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS *PHLEUM PRATENSE* ALLERGEN EXTRACT RELATIVE TO SYMPTOMATIC TREATMENT?[A]

PPAE vs. Symptomatic Treatment	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$15,414/QALY					

CE = cost-effectiveness; NA = not applicable; PPAE = *Phleum pratense* allergen extract; QALY = quality-adjusted life-year.
[a]Based on Common Drug Review reanalysis.

TABLE 15: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS *PHLEUM PRATENSE* ALLERGEN EXTRACT RELATIVE TO 5GPAE?

PPAE vs. 5GPAE	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes			X[a]			
Quality of life			X[a]			
Incremental CE ratio or net benefit calculation	Dominant					

5GPAE = 5-grass pollen allergen extract; CE = cost-effectiveness; NA = not applicable; NMA = network meta-analysis; PPAE = *Phleum pratense* allergen extract.
[a]Based on the submitted NMA, PPAE was numerically less effective in reducing symptom and medication scores than 5GPAE. However, it was assumed that PPAE would sustain efficacy for 2 years after completing 3-year treatment, while 5GPAE efficacy would be limited to the treatment period only.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 16: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 17: AUTHOR INFORMATION

Authors	Affiliations
• Cost-minimization analysis: [redacted] • Cost-utility analysis: unknown	• Health economist and outcome researcher at Merck Canada Inc. • Unknown

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

The Scottish Medicines Consortium, Scotland's health technology assessment agency, has on three separate occasions[10-12] provided a negative recommendation for Grastek for the treatment for grass pollen-induced allergic rhinitis with or without conjunctivitis, with clinically relevant symptoms and a positive skin prick test and/or a specific immunoglobulin E test to grass pollen. Summaries of these recommendations are provided below. (Note: Other European HTA agencies appear to have considered Grastek for reimbursement).

TABLE 18: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	SMC #1	SMC #2	SMC #3
Date	April 2007[10]	December 2007[11]	March 2013[12]
Drug	Standardized allergen extract of grass pollen 75,000 per oral lyophilisate (Grazax)	Standardized allergen extract of grass pollen from Timothy (*Phleum pratense*) 75,000 SQ-T per oral lyophilisate (Grazax)	Timothy grass pollen allergen (Grazax) 75,000 SQ-T oral lyophilisate
Indication	For the treatment of grass pollen-induced rhinitis and conjunctivitis in adult patients with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen	For the treatment of grass pollen-induced rhinitis and conjunctivitis in adult patients with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen	Disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen
Price	Cost for 90 days: £202.50 Cost per annum: £821.29	Not specified	Without a submission for an extension to the indication from the holder of the marketing authorization, SMC decided not to recommend Grastek for use within NHS Scotland. No further information was provided.
Treatment	Recommended dose for adults is one oral lyophilisate (75,000 SQ-T) daily		
Comparator	Rescue medication commonly available to primary care prescribers (e.g., grass or tree pollen extract injection, azelastine nasal spray, beclometasone nasal spray, budesonide nasal spray, ipratropium nasal spray, mometasone nasal spray, sodium cromoglycate nasal spray, loratadine, cetirizine, montelukast)	SCIT and symptomatic treatments including grass or tree pollen extract injection, azelastine nasal spray, beclometasone nasal spray, budesonide nasal spray, ipratropium nasal spray, mometasone nasal spray, sodium cromoglycate nasal spray, loratadine, cetirizine, montelukast	
Population modelled			
Time horizon	3 years	?	
Discount rate	Not specified	Not specified	

	SMC #1	SMC #2	SMC #3
Type of model	Cost-utility analysis (model type not reported)	Cost-utility analysis (model type not reported)	
Key outcomes	QALYs		
Results	Assuming results from the first year of the RCT also applied to the second and third year of treatment and that this treatment conferred 6 further years of benefit after treatment ended, the estimated cost per QALY gained was £9,129.	£22,597 per QALY for seasonal use compared with symptomatic treatment; £13,693 per QALY for continuous use compared with symptomatic treatment; dominance for continuous use compared with SCIT treatment.	
Sources of uncertainty	Concern about whether trial population matches modelled population. No evidence to support extrapolation of year 1 results to subsequent years. Assumption of no dropout. Majority of utility gain was outside pollen season —no robust explanation why this was seen.	Did not consider possible subgroups of severe and moderate grass pollen allergy; treatment of dropouts and inclusion of adverse events only during the pollen season rather than across the entire treatment period; questionable and non-transparent derivation of the annual QALY gain from published lit as there was no direct quality of life data available for the North European pollen season, as defined within the submission.	
CDR assessment	Although a different patient population, the model submitted to CDR appears to have been similar to the resubmission to SMC in December 2007.		

CDR = Common Drug Review; IgE = immunoglobulin E; NHS = National Health Service; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SMC = Scottish Medicines Consortium; SQ-T = Standardized Quality Tablet units.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Grastek™ - standardized allergenic extract, Timothy Grass (phleum pratense), sublingual tablet, 2800 BAU; Company: Merck Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Pointe-Claire (QC): Merck Canada Inc; 2013 Sep.
2. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008 Sep 20;372(9643):1049-57.
3. Common Drug Review. Grass pollen allergen extract (Oralair – Paladin Labs Inc.) Indication: allergic rhinitis (grass pollen). Final CDEC recommendation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013 Mar 20. [cited 2014 Apr 15]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Oralair_March-25-13_e.pdf
4. Sieber J, De Geest S, Shah-Hosseini K, Mosges R. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. Curr Med Res Opin. 2011 Apr;27(4):855-61.
5. Huovinen E, Kaprio J, Vesterinen E, Koskenvuo M. Mortality of adults with asthma: a prospective cohort study. Thorax [Internet]. 1997 Jan [cited 2014 Mar 3];52(1):49-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1758398
6. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. 2008 Dec;63(12):1624-9.
7. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. Respir Med. 2007 Sep;101(9):1885-94.
8. CDR submission binder: Oralair (grass pollen allergen extract); Company: Paladin Labs Inc. [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Paladin Labs Inc.; 2012 Sep.
9. Grastek™ (standardized allergenic extract, Timothy Grass (phleum pratense), sublingual tablet, 2800 BAU), allergy immunotherapy tablet [product monograph]. Merck Canada Inc: Kirkland (QC); 2013 Dec 12.
10. Standardised allergen extract of grass pollen from Timothy (Phleum pratense) 75,000 SQ-T per oral lyophilisate (Grazax®) No. (367/07) [Internet]. Glasgow (UK): Scottish Medicines Consortium; 2007 Apr 6. [cited 2014 Apr 15]. Available from: http://www.scottishmedicines.org.uk/files/Standardised_allergen_extract_of_grass_pollen_from_Timothy__Grazax__FINAL_April_2007_for_website.pdf
11. Re-submission: standardised allergen extract of grass pollen from Timothy (Phleum pratense) 75,000 SQ-T per oral lyophilisate (Grazax®) No. (367/07) [Internet]. Glasgow (UK): Scottish Medicines Consortium; 2007 Dec 7. [cited 2014 Apr 15]. Available from: http://www.scottishmedicines.org.uk/files/standardised_allergen_extract__Grazaz__RESUBMISSION_Final_Dec_07_for_website.pdf
12. Statement of Advice: Timothy grass pollen allergen (GRAZAX®) 75,000 SQ-T oral lyophilisate AZAX 75,000 (No: 868/13) [Internet]. Glasgow (UK): Scottish Medicines Consortium; 2013 Mar 8. [cited 2014 Apr 15]. Available from: http://www.scottishmedicines.org.uk/files/advice/timothy_grass_pollen_allergen_Grazax_Non_Submission_FINAL_March_2013_for_website.pdf